Advances in Adaptive Image Guided Brachytherapy for Cervical Cancer

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The Mr. and Mrs. H M Lui Memorial Lecture
18 December, 2015

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gynaecologic brachytherapy evolution

1905 → 1938 → (1985 →) 2000 →

mgh (TRAK)
Dose point A (R/rad/Gy)
Ref. Dimensions/Volumes (ICRU 38, 1985)
3D image based adaptive CTVs/OARs
(GEC ESTRO Rec. 2005/ICRU 88, 2015)
Limitations of 2D X-ray based BT: Point A

Identical dose point specification for large variation of tumour size and configuration
The challenge of change in tumour volume and tumour configuration during treatment

Various patterns GTV response

Corresponding patterns adaptive CTVs

ICRU/GEC ESTRO
Upcoming report 89
Fig 5.3
Concomitant Chemoradiotherapy and boost brachytherapy (OTT < 50 days)

External beam radiotherapy

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
</tr>
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</table>

Start

45 Gy

Chemotherapy

1. Cycle

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
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</table>

5-6 Cycles

Cisplatin 40 mg/m²

Brachytherapy

<table>
<thead>
<tr>
<th>Week 1</th>
<th>Week 2</th>
<th>Week 3</th>
<th>Week 4</th>
<th>Week 5</th>
<th>Week 6</th>
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HDR or PDR

$\text{EQD}_2$ 65 Gy

$\text{EQD}_2$ 85 Gy
Example: cervical cancer, FIGO IIIB: total dose 90 Gy EQD2

EBRT dose
0 Gy
18 Gy
36 Gy
EBRT45 Gy
Cisplatin (40 mg/m²) x1
Cisplatin (40 mg/m²) x2
Cisplatin (40 mg/m²) x4
Cisplatin (40 mg/m²) x5

EBRT dose
9 Gy
27 Gy
45 Gy
IGABT 45 Gy

Cervical cancer, FIGO IIIB: total dose 90 Gy EQD2

Pre-brachytherapy
Brachytherapy

GTV
CTV
Adaptive radiotherapy: typical examples

Different tumour response – Adaptation of target volume

[adaptation of dose -> high local tumour control]

At diagnosis

At brachytherapy (after 40-45 Gy EBRT-ChT)

Pötter et al. Radioth&Oncol 2011
MRI: Initial tumour extension (3D RT) pattern of response (4D RT) for adaptive MRI based planning

Dimopoulos et al. StrahlOnkol 2008
**Volumetric tumour regression: FIGO stage IIB cervical cancer, large tumor at diagnosis subgroup from EMBRACE data base, N=183/345**

**At diagnosis**

- **Good response**
  - Mean GTV: 45.2 cm³
  - Mean HR CTV: 24.6 cm³
  - N=68

- **Moderate response**
  - Mean GTV: 76.7 cm³
  - Mean HR CTV: 40.1 cm³
  - N=98

- **Poor response**
  - Mean GTV: 62.1 cm³
  - Mean HR CTV: 57.8 cm³
  - N=17

Jastaniyah N, Yoshida K et al; fellows at MUW/AKH Vienna, ASTRO 2014
The language challenge I
Risk orientated ("High Risk") adaptive Target concept

- Assessment of initial GTV and residual GTV + pathologic residual tissue based on repetitive MRI (CT/US) + clinical exam. at diagnosis and at time of Brachytherapy (40-45 Gy)
- Introduction of an initial and adaptive target concept related to the GTV: High Risk CTV-T and Intermediate Risk CTV-T

Tower of Babel: confusion of languages

Overview of the adaptive target concept cervix cancer stage IB, IIB, IIIB: HR+IR CTV-T

- Initial and residual GTV
- Res. patholog. tissue
- High Risk adaptive CTV
- Intermediate Risk CTV
- (Low Risk CTV)

GEC ESTRO Recommendations I, 2005; Upcoming ICRU/GEC ESTRO report 89, Fig. 5.9-11
The challenge of MRI availability

- **Golden standard**: *MRI at diagnosis and at brachytherapy with applicator in place* (GEC ESTRO Rec I, IV)
- **Golden standard first fraction**, *CT with appl in place next fract.* (Nesvacil et al. 2013)
- **Alternative**: *Pre brachytherapy MRI, CT with applicator in place* (Pötter et al. IJROBP 2015)
- **Complementary volumetric imaging**: *CT and US* (abdominal, vaginal, transrectal (TRUS, Schmid et al. 2015))
- **Clinical Drawing on schematic diagram always mandatory** (GEC ESTRO Rec., ICRU report 89)
Patient: - SM MUM 072 (EMBRACE study)

Clinical Drawing (IIB)

Infiltrative Exophytic

- Cervix
- Vagina
- Parametria
- Rectum or Bladder

Vagina Involvement = 0.5 cm

At Brachytherapy

w = 5 cm
h = 3 cm
t = 3 cm

From Umesh Mahantshetty, ESTRO Teaching Course 2014
MRI based (golden standard), CT based contouring (IIB)

From Umesh Mahantshetty, ESTRO Teaching Course 2014
MRI based (golden standard), CT based contouring (IIB)

From Umesh Mahantshetty, ESTRO Teaching Course 2014
MRI based (golden standard), CT based contouring (IIB)
TRUS$_{BT, \text{preBT}}$ and CT$_{BT}$ compared to MRI$_{BT, \text{preBT}}$ for the selection of HR CTV-T

Ultrasound for application guidance for HR CTV contouring complementary to CT

Intracavitary brachytherapy: FIGO stage II

Intracavitary brachytherapy: FIGO stage IIB

Target definition HR CTV-T, based on TRansrectal US

Work in progress (M. Schmid, N. Nesvacil, Vienna University)
The challenge of individualised application tailored to the individual tumour response to the vaginal and tumour topography to topography of adjacent OARs - based on pre BT clinical + imaging workup -

- Intracavitary application alone: stage IB, good response IIB
- Intracavitary application and interstitial needles:
  - large tumours with moderate or poor response
  - proximal/distal parametrial residual disease
  - large residual disease in asymmetric uterus or organs
  - unfavourable topography for OARs: for any stage
Applicator for up to mid-parametrial residual GTV and residual pathologic tissue

Kirisits et al. IJROBP 2006

Dimopoulous et al. IJROBP 2007
Applicator for up to distal parametrial residual GTV and residual pathologic tissue disease

The Vienna II Applicator

Kirisits, Berger et al. /Mahantshetty, Pötter et al. 2016

additional divergent template guided needles
The language challenge II
3D dose volume parameters
(dose points (ICRU 89))

- Dose parameters for recording and reporting of 3D image based brachytherapy
- Introduction of DVH parameters for reporting the highly inhomogeneous dose distribution of BT: CTV, OARs

GEC ESTRO Recommendations II, 2006

Radiotherapy and Oncology 75 (2006) 167-77
www.karger.com
DVH parameters targets: GTV, CTV-HR, CTV-IR

ICRU GEC ESTRO Report 89, 2015
DVH parameters and points for OARs: vagina (rectovaginal point, PIBS), bladder

Fig. 6.4, Fig. 8.8

ICRU REPORT 89
Prescribing, Recording, and Reporting Brachytherapy for Cancer of the Cervix
The New Paradigm: individual Doses in adaptive Volumes (Vienna data 1998-2008)

LR CTV-T ~ 300 cm³ ≥ 45 Gy EQD2
IR CTV-T \((D_{90})\) ~ 150 cm³ ~ 66 Gy EQD2
HR CTV-T \((D_{90})\) ~ 39 cm³ ~ 89 Gy EQD2
Res. GTV \((D_{90})\) ~ 9 cm³ ~ 119 Gy EQD2

Upcoming ICRU GEC ESTRO Rep 89
Kirisits et al. IJROBP 2005/2006;

Gyn GEC ESTRec II, 2006
Schmid et al. 2013
Clinical Evidence in IGABT Cervix Cancer

Upcoming Evidence

• Mono-intitutional cohorts (ongoing, publicat. since 2007)
• Multi-center cohorts with retrospective evaluation
  RetroEMBRACE (publications expected for 2015+)
• Prospective Trials
  STIC: comparative 2D vs. 3D (published 2012)
  EMBRACE I: observational, 08/2008 - 12/2015
  EMBRACE II: interventionalal, start 01/2016
156 patients MRI guided adaptive BT, Vienna 2001-2008, mean D90 in HR CTV 92 Gy
8 local failures, 7 pats. with G3 and 4 with G4 toxicity, (RadiothOncol 2011)
Linking DVH-parameters to clinical outcome
D90 for the HR CTV

Analysis (n=141, FIGO: IB-IVA, median follow-up=51 months)

D90 for the HR-CTV and probability of local control

- Entire population (n=141)
- Tumours > 5cm (n=76)

D90 HR CTV 90 Gy EQD2
90% probability for local control

D90 HR CTV 70 Gy EQD2
65% probability for local control

Dimopoulos et al Radioth & Oncol 2010
<table>
<thead>
<tr>
<th>Table 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes of image-guided adaptive brachytherapy in literature.</td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td><strong>Type</strong></td>
</tr>
<tr>
<td>----------------------------------</td>
</tr>
<tr>
<td>Addenbrooke's hospital UK [23]</td>
</tr>
<tr>
<td>National center Korea [14]</td>
</tr>
<tr>
<td>Vienna University Austria [20]</td>
</tr>
<tr>
<td>Tata Mumbai India [17]</td>
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<tr>
<td>STIC France [12]</td>
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<tr>
<td>Utrecht University The Netherlands [19]</td>
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<tr>
<td>Aarhus University Denmark [16]</td>
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<tr>
<td>Chiang Mai University Thailand [24]</td>
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<tr>
<td>Pittsburg medical center USA [13]</td>
</tr>
<tr>
<td>University of Leiden The Netherlands [21]</td>
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<tr>
<td>Medical college Wisconsin USA [15]</td>
</tr>
<tr>
<td>University of Melbourne Australia [18]</td>
</tr>
<tr>
<td>University of California, San Diego, USA [22]</td>
</tr>
<tr>
<td>Gustave Roussy villejuif France (this study)</td>
</tr>
</tbody>
</table>

N: number of patients, HDR: high dose rate, PDR: pulsed-dose rate, NR: not reported, US ultrasound.
Multicenter trials
Speaking the same language representing advanced RT

- RetroEMBRACE:
  - Retrospective Analysis of IGABT
  - 731 patients from 12 centers

- EMBRACE I
  - Prospective observational clinical trial on the effects of IGABT
  - >1350 patients from 24 centers (from 2008-2015)

- Common approach for contouring of CTV and OARs
- Common language for reporting variations in fractionated treatment (in terms of equivalent dose: EQD2)
  - 3-5 fractions of HDR (5-7 Gy per fraction)
  - 1-2 fractions of PDR (15-30 Gy per fraction)
### Severity

<table>
<thead>
<tr>
<th>Severity</th>
<th>Proctitis</th>
<th>Bleeding</th>
<th>Stenosis</th>
<th>Fistula</th>
<th>ALL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 1-4</td>
<td>0.733</td>
<td>&lt; 0.0001</td>
<td>NS</td>
<td>&lt; 0.0001</td>
<td>0.009</td>
</tr>
<tr>
<td>Grade 2-4</td>
<td>0.032</td>
<td>0.001</td>
<td>NS</td>
<td>&lt; 0.0001</td>
<td>&lt; 0.0001</td>
</tr>
<tr>
<td>Grade 3-4</td>
<td>0.123</td>
<td>0.042</td>
<td>NS</td>
<td>&lt; 0.0001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

### Probability of grade 2-4 rectal morbidity

<table>
<thead>
<tr>
<th>Probability</th>
<th>Grade 2-4 rectal morbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.00</td>
<td>0.00</td>
</tr>
<tr>
<td>0.02</td>
<td>0.02</td>
</tr>
<tr>
<td>0.04</td>
<td>0.04</td>
</tr>
<tr>
<td>0.06</td>
<td>0.06</td>
</tr>
<tr>
<td>0.08</td>
<td>0.08</td>
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</tbody>
</table>

**D2cm³ (Gy, EqD2 α/β=3 Gy)**

- < 55 Gy
- 55-60
- 60-65
- 65-70
- 70-75
- ≥ 75 Gy

### EMBRACE

- N=960 patients
- Median follow-up 25 mths
- G1: 135, G2: 39, G3: 4; total 782

### Bleeding

- G1: 114, G2: 31, G3: 10; total 805

**Fistula**

- G2: 5, G3: 3, G4: 1; total 951

Mazeron et al, under publication
Dose Effects: vaginal morbidity
multi-centre data, prospective (EMBRACE)
ICRU recto-vaginal point (ICRU 89)

Vaginal morbidity
(shortening /stenosis)
dose effect in 446 patients
(EMBRACE, physician reported outcome)
(Kirchheiner et al, ESTRO Geneva 2013,
submitted Radioth & Oncol)
Bladder (EMBRACE and Paris)

- Data extraction Oct 2013 (EMBRACE)
- All endpoints except ureter stenosis

Paris: Mazeron et al. 2014, Brachytherapy

Nkiwane et al. 2015 Brachytherapy

>80Gy: 30-40%

<80Gy: 15-30%
# Results:

<table>
<thead>
<tr>
<th>Variable</th>
<th>No of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median Age (years)</td>
<td>53 (23 – 91)</td>
</tr>
<tr>
<td>FIGO Stage</td>
<td></td>
</tr>
<tr>
<td>1A</td>
<td>2 (0.3%)</td>
</tr>
<tr>
<td>1B</td>
<td>123 (16.8%)</td>
</tr>
<tr>
<td>2A</td>
<td>42 (5.7%)</td>
</tr>
<tr>
<td>2B</td>
<td>368 (50.3%)</td>
</tr>
<tr>
<td>3A</td>
<td>23 (3.1%)</td>
</tr>
<tr>
<td>3B</td>
<td>145 (19.8%)</td>
</tr>
<tr>
<td>4A</td>
<td>25 (3.1%)</td>
</tr>
<tr>
<td>4B</td>
<td>5 (0.7%)</td>
</tr>
<tr>
<td>Histology</td>
<td></td>
</tr>
<tr>
<td>Squamous cell Ca</td>
<td>620 (84.8%)</td>
</tr>
<tr>
<td>Adenocarcinoma</td>
<td>71 (9.7%)</td>
</tr>
<tr>
<td>Adenosquamous</td>
<td>29 (4%)</td>
</tr>
<tr>
<td>Others</td>
<td>11 (1.5%)</td>
</tr>
<tr>
<td>Median tumour width</td>
<td></td>
</tr>
<tr>
<td>Clinically: 50 mm</td>
<td></td>
</tr>
<tr>
<td>MRT @ diagnosis: 47 mm</td>
<td></td>
</tr>
<tr>
<td>Nodal status</td>
<td></td>
</tr>
<tr>
<td>N+</td>
<td>296 (40%)</td>
</tr>
<tr>
<td>N-</td>
<td>436 (60%)</td>
</tr>
<tr>
<td>CHT</td>
<td></td>
</tr>
<tr>
<td>Yes: 566 (76.5%)</td>
<td>No: 165 (22.5%)</td>
</tr>
<tr>
<td>Median FU</td>
<td>47 months</td>
</tr>
</tbody>
</table>
Local, pelvic and distant control, cancer specific and overall survival

Vienna (2011) 3y:
- Loc failure 5%
- Pelv failure 9%
- Syst failure 18%

Vienna: mean 92 Gy HR CTV

Mean D90 HR CTV 84 Gy

Sturdza et al. Submitted
Local control and FIGO stage (RetroEMBRACE)

Local failure

RetroEMBRACE

3y

IB 2%*
IIB 7-9%
IIIB 21-25%
IVA 24%

*2 events in IB2

Local failure

Vienna (2011)

3y

IB 0%
IIB 4%
IIIB 14%
IVA 2/6 (n)

Sturdza et al. 2015
Dose, volume, treatment time and local control (n=462)

More dose is needed for large HR CTV

Prolongation of OTT by 7 days

is equivalent to decreasing CTV_{HR} dose by 5Gy.

Relationship between EBRT-C+BT dose and local control from retroEMBRACE, n=462 patients (Tanderup et al, submitted to JCO)
Local control – advanced treatment adaptation including interstitial brachytherapy

<table>
<thead>
<tr>
<th>Width in MRI at diagnosis</th>
<th>Local control at 5 year (%)</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Limited adaptation</td>
</tr>
<tr>
<td>Tumor &lt;5cm</td>
<td>95%</td>
</tr>
<tr>
<td>Tumor ≥5cm</td>
<td>77%</td>
</tr>
</tbody>
</table>

The use of advanced adaptation including interstitial BT improves local control in large tumors

Fokdal et al. and Fortin et al. to be submitted
Interpretation of RetroEMBRACE results (IGABT compared to large population based cohorts 2D BT)

<table>
<thead>
<tr>
<th>Pelvic failure (crude)</th>
<th>Concomitant chemo</th>
<th>IB</th>
<th>IIB</th>
<th>IIIB</th>
<th>total</th>
</tr>
</thead>
<tbody>
<tr>
<td>retroEMBRACE (n=731)</td>
<td>77%</td>
<td>4%</td>
<td>11%</td>
<td>25%</td>
<td>13%</td>
</tr>
<tr>
<td>Perez 1998</td>
<td>0%</td>
<td>12%</td>
<td>21%</td>
<td>41%</td>
<td>23%</td>
</tr>
<tr>
<td>Barillot 1997</td>
<td>0%</td>
<td>13%</td>
<td>24%</td>
<td>49%</td>
<td></td>
</tr>
<tr>
<td>Improvement</td>
<td>Δ8-9%</td>
<td>Δ10-13%</td>
<td>Δ16-24%</td>
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</table>

Overall Survival Radio-chemo

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</thead>
<tbody>
<tr>
<td>No of pts</td>
<td>394</td>
<td>471</td>
<td>3246</td>
<td>2571</td>
</tr>
<tr>
<td>5y OS</td>
<td>67%</td>
<td>55%</td>
<td>55%</td>
<td>54%</td>
</tr>
<tr>
<td>Improvement</td>
<td>Reference</td>
<td>Δ12%</td>
<td>Δ12%</td>
<td>Δ13%</td>
</tr>
</tbody>
</table>
Number and location of nodal failures (EMBRACE) (cohort n=1077)

Nomden et al 2015
Systemic (distant) recurrence analysis
(EMBRACE data, 133 events in 753 patients)

Systemic recurrences at first event

Brain: 2%
Supraclavicular nodes: 5%
Lungs: 33%
Paraaortic nodes: 42%
Peritoneal carcinomatosis: 8%
Inguinal nodes: 6%
Liver: 9%
Bone: 11%
Others nodes: 18%
Others organs: 5%

Fortin et al. ASTRO 2015
Overall Survival in locally advanced cervical cancer: the impact of brachytherapy

Total
25% increase in Overall Survival
from "no brachy" to "2D brachy" (Han)
to "4D brachy" (RetroEMBRACE)

Han et al Int J Radiation Oncol Biol Phys 2013;87:111-119
Sturdza et al. Improved local control and survival in LACC through Imae guided adaptive brachytherapy, submitted
Cervical Cancer FIGO IIIB

High Risk CTV = HRCTV

IGABT = Image Guided Adaptative Brachytherapy

GTV

IRCTV
Next generation of clinical trials based on IGABT + IGRT as RCT

- Hypothesis driven -

- Comparative Trials on IGABT vs. 2D (randomized (??))
- Dose escalation for advanced disease HR CTV (LC, OS)
- Dose de-escalation for limited and favourable advanced disease (good response,...) (Morb/QoL)
- Para-aortic RT, Lymphnode Boost (NC, OS)
- Systematic concomitant radiochemotherapy min. 5 cycl. for subgroups with high risk of distant metastases (OS)
- Testing Dose/Volume constraints for Target and OARs
- Biomarker investigation (Hypoxia, HPV, EGFR, VEGF..)
EMBRACE II
Start 1/2016

MRI guided adaptive brachytherapy (IGABT)

Residual Gross Tumor
D98 >>95Gy
High Risk Target
D90 >90Gy
Intermediate Risk Target > 60Gy
Bladder D2cc = 76Gy (< 80Gy)
Rectum D2cc = 64Gy (< 65Gy)
Sigmoid D2cc = 61Gy (< 70Gy)

Nodal CTV-E based on Risk Group

Initial GTV
GTV
CTV
CTV
CTV
CTV
CTV

Residual GTV-T, Adaptive HR CTV-T, IR CTV-T

+ Para-aortic
Large pelvis
Small pelvis

High Risk
Intermediate Risk
Low Risk

EBRT  Chemotherapy  Brachy
week 1  week 2  week 3  week 4  week 5  week 6  week 7

RChTh + BT in < 50 days

IMRT + IGRT

CTV-N  PTV-
Initial GTV-T  Initial HR CTV-T

Start 1/2016
General aims for EMBRACE II

• To systematically apply advanced image guided EBRT and adaptive BT (IC/IS) in a prospective multicentre setting

• To systematically implement a dose prescription protocol with specific dose constraints for target volumes (GTV, CTV_{HR} and OARs (high, intermediate and low dose volumes) applied in ≤50 days

• To apply for EBRT individualised risk adapted target concepts and lymph node boosting

• To systematically administer simultaneous chemotherapy to EBRT, in particular in high risk patients

• To benchmark an outstanding high level of local, nodal, systemic control and survival as well as a low incidence of intermediate and major morbidity and QOL

www.meduniwien.ac.at
Target concepts EMBRACE II, EBRT

CTV-E based on risk of spread

CTV-T LR (CT/MRI), ITV-T LR, CTV-E, PTV 45 (T+E)
Motivation for reduced margins: reduction of morbidity “orange and the peel...50% vs. 50% volume”, no evidence for nodal recurrence at margins (except cranial)

<table>
<thead>
<tr>
<th></th>
<th>CTV-E</th>
<th>CTV-E + 5mm</th>
<th>CTV-E + 10mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>~1000 cc</td>
<td>~1500 cc</td>
<td>~2000 cc</td>
<td></td>
</tr>
<tr>
<td>43Gy vol -&gt;</td>
<td>~1700 cc</td>
<td>~2200 cc</td>
<td></td>
</tr>
</tbody>
</table>

Diarrhoea Dose response curve (EMBRACE)
## Planning aims and Dose prescription (I)

### CTV-T EMBRACE II protocol (EBRT+BT) (1/2016)

<table>
<thead>
<tr>
<th></th>
<th>D90 CTV\textsubscript{HR} EQD\textsubscript{2,10}</th>
<th>D98 CTV\textsubscript{HR} EQD\textsubscript{2,10}</th>
<th>D98 GTV EQD\textsubscript{2,10}</th>
<th>D98 CTV\textsubscript{IR} EQD\textsubscript{2,10}</th>
<th>D Point A EQD\textsubscript{2,10}</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Planning Aims</strong></td>
<td>&gt; 90 Gy &lt; 95 Gy</td>
<td>&gt; 75 Gy</td>
<td>&gt;95 Gy</td>
<td>&gt; 60 Gy</td>
<td>&gt; 65 Gy</td>
</tr>
<tr>
<td><strong>Limits for Prescribed Dose</strong></td>
<td>&gt; 85 Gy</td>
<td>-</td>
<td>&gt;90 Gy</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Planning aims and Dose prescription (II)
OAR EMBRACE II protocol (EBRT+BT) (1/2016)

<table>
<thead>
<tr>
<th></th>
<th>Bladder $D_{2cm^3}$</th>
<th>Rectum $D_{2cm^3}$ EQD2&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Recto-vaginal point EQD2&lt;sub&gt;3&lt;/sub&gt;</th>
<th>Sigmoid/ Bowel $D_{2cm^3}$ EQD2&lt;sub&gt;3&lt;/sub&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Planning Aims</td>
<td>&lt; 80 Gy</td>
<td>&lt; 65 Gy</td>
<td>&lt; 65 Gy</td>
<td>&lt; 70 Gy</td>
</tr>
<tr>
<td>Limits for Prescribed Dose</td>
<td>&lt; 90 Gy</td>
<td>&lt; 75 Gy</td>
<td>&lt; 75 Gy</td>
<td>&lt; 75 Gy</td>
</tr>
</tbody>
</table>
In EMBRACE II, the improved therapeutic window (through increased application of IC/IS) will be exploited for ... the incidence of bowel morbidity and with a potential also to be beneficial for urinary morbidity.
General endpoints for EMBRACE II (www.embracestudy.dk)

Hypothesis for Overall Survival (OS):

- Overall cohort: 81% (3 years) / 71% (5 years) (improvement of 4%)
- Stage I, II and N-: 88% (3 years) / 83% (5 years) (improvement of 1%)
- Stage III, IV or N+: 71% (3 years) / 56% (5 years) (improvement of 7%)

Improvement by prescription protocol for IGRT EBRT and IGABT
- reduced local failures in patients with adaptive CTV-T HR > 30cm²
- improved nodal control in high risk patients (Stage III, IV or N1)
- improved systemic control

+ Reduction of morbidity: prescribed dose constraints
  by dose de-escalation in low risk patients (Stage I, II and N0)
  by margin reduction for CTV-E (5 mm) in all patients (IMRT, IGRT)
Acknowledgements

Gyn GEC ESTRO network

EMBRACE study and research group

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4th Annual EMBRACE meeting Vienna 12/2012

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